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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,718	12/14/2001	Karl H. Weisgraber	UCAL-222	5282

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,718	WEISGRABER ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,7,14,15 and 20-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,7,14,15 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/31/05 has been entered.

Applicants' Amendment and Response, filed 3/31/05, has been entered. Claim 1 has been amended. Claim 23 has been cancelled. Claims 1, 3, 5, 7, 14, 15, 20-22 are pending and under current examination.

The Weisgraber Declaration (under 37 CDF § 1.132), filed 2/25/02, has been considered.

Information Disclosure Statement

Applicants' IDS, filed 12/3/04, has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5, 7, 14, 15, 20-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse

whose genome comprises a homozygous modification of the endogenous apolipoprotein E (apoE), wherein said modified allele comprises an apoE-encoding nucleic acid under transcriptional control of endogenous regulatory sequences, wherein the modified allele encodes a modified apoE polypeptide that exhibits domain interaction characteristic of human apoE4, wherein the modified endogenous mouse apoE polypeptide comprises a Thr → Arg substitution at a position equivalent to amino acid 61 of human apoE4, wherein the modified apoE polypeptide exhibits preferential binding to lower density lipoproteins, wherein the mouse exhibits apoE4-related neurodegeneration, cells isolated from said mouse, an methods of identifying an agent that reduces a phenomenon associated with apoE4-related neurodegeneration by contacting said mouse with a test agent, and determining the effect of the test agent on reducing the apoE4-related neurodegeneration, does not reasonably provide enablement for the breadth of the mice (including homozygous and heterozygous) and methods of using these mice in methods of identifying an agent that reduces a phenomenon associated with Alzheimer's disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants present the Weisgraber declaration as evidence that the claimed transgenic mice would be able to be used in the screening method of claim 14. Particularly, Applicants argue that the specification provides sufficient guidance

with regard to apoE-related neurological disorders, such as AD, poor outcome following stroke/head injury and cerebral ischemia. See p. 5 of the Response and paragraph 0050. Furthermore, Applicants argue that apoE-related neurological disorders can be assessed by pathological studies, including assessment of neurodegeneration. Particularly, Applicants argue that the instant specification states that phenomena associated with apoE4-associated disorders includes high serum cholesterol levels. See pp. 5-6, bridging ¶. Applicants argue that the specification teaches data showing that the gene target mouse, as instantly claimed, produces a modified apoE protein, and that this protein exhibits preferential binding to LDLs, and that this mouse can be used as a model for human apoE4 domain interaction. See p. 6, 3rd ¶ of the Response. Applicants point to the Weigraber Declaration, which provides evidence that the claimed mice exhibit a degree of neurodegeneration that is greater than a control mouse, and thus, that this Declaration provides support that this mouse is useful for identifying agents that treat apoE4-related neurodegeneration. See p. 6, 4th ¶. Finally, Applicants argue that the instant specification provides sufficient enablement to identify an agent that reduces a phenomenon associated with Alzheimer's disease because the claimed mice exhibit a degree of neurodegeneration greater than a control mouse. See p. 7.

Applicants' arguments and the Weisgraber Declaration are found to be partially persuasive. The Weisgraber Declaration states that the assessment of

neurodegeneration between wild type and Arg-61 mice was made by examination of presynaptic terminal density. The Declaration states that there is a significant decrease in the presynaptic terminal density in the Arg-61 mice, when compared to wild-type mice, and that this indicates neurodegeneration in the one-year old Arg-61 mice. See p. 4 and accompanying figure of the Declaration. The Declaration is not fully persuasive because it is unclear if the Arg-61 mice are homozygous or heterozygous mice. The specification teaches the generation of heterozygous and homozygous targeted mice and the analysis of these mice. For example, ¶ 00192 of the specification teaches the isoelectric focusing of wt/wt; wt/Arg-61 and Arg-61/Arg-61 mice. The specification teaches that the Arg-61 in the heterozygous mice was reduced by approximately 70%. The specification further teaches that the distribution of lipoprotein fractions from the heterozygous mouse plasma was examined. See p. 56, ¶ 00195. Thus, it is unclear if the phenotype of ApoE4-related neurodegeneration is associated with the heterozygous or homozygous mouse, or both.

With specific regard to claims 14 and 15 (methods of utilizing the claimed mice in methods of identifying an agent that reduces the phenomenon associated with AD), these methods are not enabling for their breadth because the mice that are used in the claims have one phenomenon, neurodegeneration, which is a phenomenon that is associated with other disorders. Applicants have clearly stated this, by pointing to the specification, which shows various ways in which

neurodegeneration can occur such as AD, poor outcome following stroke/head injury and cerebral ischemia. The mice exhibit two particular phenotypes, a modified apoE polypeptide that exhibits preferential binding to LDLs, and apoE4-related neurodegeneration. Thus, the breadth of the using the mice in identifying agents that reduce a phenomenon in AD is not found to be enabled because the mice exhibit neurodegeneration, which may or may not be caused by AD. Furthermore, claim 15, which recites that the phenomenon associated with AD is: amyloid deposits, neuronal cell loss, and neurofibrillary tangles, is not found to be enabling because the claimed mice do not appear to exhibit any of these phenotype, and thus, could not be used in these methods.

Accordingly, in view of the lack of teachings or guidance provided by the specification with regard to utilizing the mice in methods of identifying an agent that reduces a phenomenon associated with Alzheimer's disease, the lack of clarification as to whether homozygous or heterozygous mice exhibit the ApoE4-related neurodegeneration, the state of the art, which teaches that apoE4-related neurodegeneration can be caused by factors other than Alzheimer's disease, it would have required undue experimentation for one of skill in the art to use the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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